REMARKS

Claims 1-9, 11-12, 14-15, 17-19, 23, and 27-65 were pending in the instant case and were ALLOWED. In lieu of paying the issue fee, Applicants file herewith an RCE and the instant Amendment. Claims 1, 29, 31, 33, 37, 40 and 48-52 have been amended to recite that the peptide featured in the instant claims can be a "retro-inverso" form of the peptide having the recited structural characteristics. This subject matter is of significant commercial value to the instant claims in that such peptide forms are commonly-used peptide mimetics having advantageous molecular properties in the therapeutic peptide art, i.e., *in vivo* stability. As the Examiner is well aware, the vast majority of naturally occurring polypeptides are composed of L-amino acids. Because such peptides are prone to proteolytic degradation, however, this can limit their therapeutic application. By contract, the *in vivo* proteolytic machinery is not well equipped to deal with D-amino acid polypeptides. Accordingly, it is well known in the art that inversion of the stereochemistry of the peptide, accompanied by chain reversal, can yield proteolytically stable retro-inverso peptide isomers whose side chain topology corresponds closely to that of a native sequence, and whose biological activity emulates that of a parent polypeptide.

Applicants also submit herewith, for the Examiner's consideration, a publication by the instant inventors describing the *in vivo* stability and biological activity of the peptides of the instant invention. See Michod *et al.* (2009) J. Natl. Cancer Inst., 101:828-832. In this article, the inventors describe a retro-inverso form of the RasGAP-derived peptide (TAT-RasGAP(317-326)) which was previously shown to specifically sensitize tumor cells to genotoxin-induced apoptosis *in vitro*. (See also the Working Examples of the instant specification.) The article describes the *in vivo* stability of the retro-inverso peptide (a protease-resistant D-form of the peptide), RI.TAT-RasGAP(317-326), and it's *in vivo* efficacy in a mouse tumor model. In particle the article teaches that:

> After intraperitoneal injection, RI.TAT-RasGAP(317-326) persisted in the blood of nude mice for more than 1 hour and was detectable in various tissues and subcutaneous tumors. Tumor-bearing mice treated daily for 7 days with RI.TAT-RasGAP(317-326) (1.65 mg/kg body weight) and cisplatin (0.5 mg/kg body weight) or doxorubicin (0.25 mg/kg body weight) displayed reduced tumor growth compared with those treated with either genotoxin alone (n = 5-7 mice per group; P = .004 and P = .005, respectively; repeated measures analysis of

> variance [ANOVA, two-sided]). This ability of the RI.TAT-RasGAP(317-326) peptide to enhance the tumor growth inhibitory effect of cisplatin was still observed at peptide doses that were at least 150-fold lower than the dose lethal to 50% of mice. (see Abstract)

The article provides support for the art-recognized principle that retro-inverso isoforms of biologically active peptides have increased *in vivo* stability and retain biological activity, making them art-appreciated mimetics for therapeutic peptide use.

It is Applicant's position that amendment of the claims to include such peptides clarifies the intended claimed subject matter and introduces no mew matter. Support for the amendment can be found, at least for example, at page 14, line 25 through page 15, line 12, as well as in claims 4 and 8 of the application as originally filed.

Applicant respectfully submits that the instant claims are in condition for allowance. If there are any questions regarding the proposed amendments to the application, we invite the Examiner to call Applicant's representative at the telephone number below.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. KZY-004RCE.

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Respectfully submitted,

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